

WHAT IS CLAIMED IS:

1 1. A transgenic nonhuman mammal comprising two human
2 immunoglobulin loci, wherein one of two said human immunoglobulin loci is a human heavy
3 chain locus and the other locus is a human light chain locus; and
4 wherein only one of said loci is of a transchromosome.

1 2. The transgenic nonhuman mammal of claim 1, wherein the
2 transchromosome is autonomous.

1 3. The transgenic nonhuman mammal of claim 1, wherein the human
2 light chain locus is associated with an endogenous mammalian chromosome.

1 4. The transgenic nonhuman mammal of claim 1, wherein the human
2 heavy chain locus is of a transchromosome and the human light chain locus is associated with
3 an endogenous mammalian chromosome.

1 5. The transgenic nonhuman mammal of claim 1, wherein the human
2 light chain locus is of a transchromosome and the human heavy chain locus is associated with
3 an endogenous mammalian chromosome.

1 6. The transgenic nonhuman mammal of claim 1, wherein the
2 endogenous mammalian heavy chain locus and at least one mammalian light chain locus are
3 inactivated.

1 7. The transgenic nonhuman mammal of claim 6, wherein the
2 endogenous mammalian heavy chain locus and kappa light chain locus are inactivated.

1 8. The transgenic nonhuman mammal of claim 4, wherein at least a part
2 of the human light chain locus is cloned into a YAC vector.

1 9. The transgenic nonhuman mammal of claim 1, wherein the transgenic
2 nonhuman mammal is a mouse.

1 10. The transgenic nonhuman mammal of claim 1, wherein the
2 transchromosome comprises a fragment of human chromosome 14.

1 11. The transgenic nonhuman mammal of claim 1, wherein the human
2 heavy chain locus is comprised in hCF(SC20) and the human light chain locus is comprised
3 in the human kappa light chain locus transgene KCo5.

1 12. A method for generating a plurality of B cells expressing human
2 antibody sequences, the method comprising:
3 providing the transgenic nonhuman mammal of claim 1; and
4 immunizing the transgenic nonhuman mammal to generate a plurality of B
5 cells expressing human antibody sequences.

1 13. The method of claim 12, further comprising collecting the plurality of
2 B cells expressing sequences expressing human antibodies.

1 14. The method of claim 13, further comprising fusing the plurality of B
2 cells with immortalized cells to form hybridomas.

1 15. The method of claim 14, further comprising collecting the human
2 antibody sequences from the hybridomas.

1 16. The method of claim 15, wherein the human antibody sequences are
2 purified.

1 17. The method of claim 12, further comprising collecting the sequences
2 encoding human antibodies.

1 18. The method of claim 17, wherein the sequences encoding human
2 antibodies are full length.

1 19. The method of claim 18, further comprising expressing the sequences
2 in a transfected cell.

1 20. The method of claim 12, wherein the transchromosome is a fragment
2 of human chromosome 14.

1 21. The method of claim 12, wherein the human transchromosome is
2 hCF(SC20).

1 22. The method of claim 12, wherein the human light chain locus
2 comprises unrearranged sequences from the natural human kappa light chain locus.

1 23. The method of claim 12, wherein the human kappa light chain locus is
2 the inserted KCo5 transgene.

1 24. The method of claim 12, wherein the plurality of B cells comprises at
2 least a first B cell encoding an antibody with a first isotype selected from the group consisting
3 of IgA, IgD, IgE, IgG and IgM.

1 25. The method of claim 24, wherein the plurality of B cells further
2 comprises at least a second B cell encoding an antibody with a second isotype different from
3 the first isotype selected from the group consisting of IgA, IgD, IgE, IgG and IgM.

1 26. The method of claim 12, wherein the plurality of B cells comprise at
2 least five B cells each encoding an antibody having a different isotype wherein the isotypes
3 of the antibodies are IgA, IgD, IgE, IgG and IgM respectively.

1 27. The method of claim 24, wherein the IgA isotype is IgA₁ or IgA₂.

1 28. The method of claim 24, wherein the IgG isotype is IgG₁, IgG₂, IgG₃
2 or IgG₄.

1 29. A method for generating a human sequence antibody that binds to a
2 predetermined antigen, the method comprising the following steps:
3 immunizing the transgenic nonhuman mammal of claim 1 with the
4 predetermined antigen; and
5 collecting the human sequence antibody from the immunized transgenic
6 nonhuman mammal.

1 30. The method of claim 29, wherein the human sequence antibody binds
2 to a predetermined antigen with an equilibrium association constant (K_a) of at least 10^{10} M^{-1} .

1 31. The method of claim 29, wherein the human sequence antibody binds
2 to a predetermined antigen with an equilibrium association constant (K_a) of at least 10^9 M^{-1} .

1 32. The method of claim 29, wherein the human sequence antibody binds
2 to a predetermined antigen with an equilibrium association constant (K_a) of at least 10^8 M^{-1} .

1 33. The method of claim 29, wherein the human sequence antibodies are
2 monoclonal.

1 34. The method of claim 29, wherein the human sequence antibody is a
2 F(ab')_2 , Fab, F_v , or F_d fragment.

1 35. The method of claim 29, wherein the human sequence antibody is
2 antigen-specific.

1 36. A method for generating antigen-specific hybridomas secreting human
2 sequence antibody, the method comprising:
3 immunizing the transgenic nonhuman mammal of claim 1 with a
4 predetermined antigen;
5 fusing lymphocytes from the transgenic nonhuman mammal with
6 immortalized cells to form hybridoma cells; and
7 determining the binding of the antibody produced by the hybridoma cells to
8 the predetermined antigen.

1 37. The method of claim 36, wherein greater than 50% of the antigen-
2 specific hybridoma clones secrete antibody having human heavy chain and human light
3 chain.

1 38. A method for generating a human sequence antibody that binds to a
2 predetermined antigen, the method comprising the following steps:
3 immunizing the transgenic nonhuman mammal of claim 1 with the
4 predetermined antigen; and
5 screening hybridoma cells formed for the presence of antigen reactive
6 antibodies.

1 39. The method of claim 38, wherein the hybridoma cells are subcloned at
2 an efficiency of greater than 20%.

1 40. The method of claim 38, wherein the antigen reactive antibodies are
2 secreted from the hybridoma in culture.

1 41. The method of claim 38, wherein the antigen reactive antibodies are
2 substantially pure.

1 42. The method of claim 41, wherein the substantially pure antibodies are
2 formulated for therapeutic use.

1 43. A method for producing rearranged immunoglobulin sequences
2 comprising:
3 providing the transgenic nonhuman mammal of claim 1, and
4 obtaining the rearranged immunoglobulin sequences from the transgenic
5 nonhuman mammal.

1 44. The method of claim 43, wherein the obtaining step comprises
2 collecting B cell lymphocytes containing the rearranged immunoglobulin sequences from the
3 transgenic nonhuman mammal.

1 45. The method of claim 43, wherein the obtaining step comprises
2 isolating and amplifying mRNA from B cell lymphocytes to generate cDNA.

1 46. The method of claim 45, further comprising isolating and amplifying
2 heavy and light chain variable region sequences from the cDNA.

1 47. An isolated nucleic acid encoding the heavy and light chain variable
2 region sequences of claim 46.

1 48. An isolated nucleic acid encoding the heavy chain variable region
2 sequences of claim 46.

1 49. An isolated nucleic acid encoding the light chain variable region
2 sequences of claim 46.

1 50. A vector comprising the nucleic acid of claim 47.

1 51. An expression vector comprising the nucleic acid of claim 47 in which
2 the heavy and light chain variable regions sequences of the nucleic acid are operatively linked
3 with a regulatory sequence that controls expression of the nucleic acid in a host cell.

1 52. A host cell comprising the nucleic acid of claim 47, or progeny of the
2 cell.

1 53. The host cell of claim 52 which is a eukaryote.

1 54. The method of claim 43, further comprising:
2 culturing the host cell of claim 52 under conditions such that the nucleic acid
3 is expressed; and
4 recovering the nucleic acid from the cultured host cell or its cultured medium.

1 55. A method of producing a human antibody display library, the method
2 comprising:
3 introducing an immunogen into the transgenic nonhuman mammal of claim 1;
4 isolating a population of nucleic acids encoding human antibody chains from
5 lymphatic cells of the nonhuman transgenic animal; and
6 forming a library of display packages displaying the antibody chains, wherein
7 a library member comprises a nucleic acid encoding an antibody chain, and the antibody
8 chain is displayed from the package.

1 56. The method of claim 55 wherein the nonhuman transgenic mammal
2 lacks a detectable titer to the immunogen when the isolating step is performed.

1 57. The method of claim 55, wherein the immunogen is a nucleic acid.

1 58. The method of claim 55, wherein the nucleic acid encodes a membrane
2 bound receptor.

1 59. A method for generating a human sequence antibody, or fragment
2 thereof, that binds to a predetermined antigen, the method comprising the following steps:
3 immunizing the transgenic nonhuman mammal of claim 1 with the
4 predetermined antigen;

5 collecting antibody V region sequences from the immunized transgenic
6 nonhuman mammal;
7 cloning the collected V regions into a DNA vector generating an expression
8 library; and
9 expressing the library to identify V region sequences that encode an antibody,
10 or fragment thereof, that binds to the predetermined antigen.

1 60. A method for generating a human sequence antibody or fragment
2 thereof, that binds to a predetermined antigen, the method comprising the following steps:
3 immunizing the transgenic nonhuman mammal of claim 1 with the
4 predetermined antigen;
5 isolating cDNA coding at least one human antibody V region from B cells of
6 the immunized transgenic nonhuman mammal or from hybridomas generated by fusion of
7 said B cell and an immortalized cell;
8 cloning said cDNA into an expression vector;
9 introducing said vector into a host cell;
10 culturing said host cell; and
11 collecting said human sequence antibody or fragment thereof from said host
12 cell or culture medium thereof.

1 61. The method of claim 60, wherein the isolating step is performed by
2 PCR.

1 62. The method of claim 60, wherein the isolating step is performed by
2 cDNA library screening using at least one DNA probe.

1 63. The method of claim 60, wherein the isolating step is performed by
2 phage display library screening.

1 64. The method of claim 60, wherein the cDNA encodes full length human
2 antibody sequences.

1 65. The method of claim 60, wherein the collected human sequence
2 antibody isotype is different from the isotype of antibody producing cells of said immunized
3 transgenic nonhuman mammal.

1 66. A method of improving the stability of a transchromosomic mouse
2 hybridoma cell expressing a human antibody reactive with a predetermined antigen, the
3 method comprising:
4 breeding a first mouse, the first mouse comprising a first human
5 immunoglobulin locus on a transchromosome, together with a second mouse, the second
6 mouse comprising a second human immunoglobulin locus inserted within an endogenous
7 mouse chromosome;
8 obtaining a third mouse from the breeding, the third mouse comprising both
9 the first and the second human immunoglobulin loci;
10 immunizing the third mouse, or its progeny, with the predetermined antigen;
11 collecting B cells from the immunized mouse; and
12 fusing the B cells with immortalized cells to obtain hybridoma cells
13 expressing the human antibody reactive with the predetermined antigen.

1 67. The method of claim 66 further comprising:
2 culturing the hybridoma cells in media;
3 testing the media to identify the presence of hybridoma cells that express
4 human antibodies reactive with the predetermined antigen;
5 diluting the hybridoma cells; and
6 culturing the diluted hybridoma cells to obtain clonal cell lines expressing a
7 monoclonal human antibody reactive with the predetermined antigen.

1 68. The method of claim 67 wherein the clonal cell lines are obtained from
2 at least 50% of the identified hybridoma cells.

1 69. A mouse hybridoma cell secreting a human sequence antibody having
2 an IgA isotype that binds to a specified antigen with an equilibrium association constant (K_a)
3 of at least 10^{10} M^{-1} .

1 70. A human sequence antibody having an IgA isotype that binds to a
2 specified antigen with an equilibrium association constant (K_a) of at least 10^{10} M^{-1} .

1 71. The transgenic nonhuman mammal of claim 1, further comprising a
2 mutation of a gene, wherein the mutation increases the immune response to autoantigen.

1 72. The transgenic nonhuman mammal of claim 71, wherein the mutation
2 is the inactivation of the Fc-gamma IIB gene.

1 73. The method of claim 12, further comprising a mutation of a gene,
2 wherein the mutation increases the immune response to autoantigen.

1 74. The method of claim 73, wherein the mutation is the inactivation of the
2 Fc-gamma IIB gene.

1 75. The method of claim 29, further comprising a mutation of a gene,
2 wherein the mutation increases the immune response to autoantigen.

1 76. The method of claim 75, wherein the mutation is the inactivation of the
2 Fc-gamma IIB gene.

1 77. The method of claim 36, further comprising a mutation of a gene,
2 wherein the mutation increases the immune response to autoantigen.

1 78. The method of claim 77, wherein the mutation is the inactivation of the
2 Fc-gamma IIB gene.

1 79. The method of claim 38, further comprising a mutation of a gene,
2 wherein the mutation increases the immune response to autoantigen.

1 80. The method of claim 79, wherein the mutation is the inactivation of the
2 Fc-gamma IIB gene.

1 81. The method of claim 43, further comprising a mutation of a gene,
2 wherein the mutation increases the immune response to autoantigen.

1 82. The method of claim 81, wherein the mutation is the inactivation of the
2 Fc-gamma IIB gene.

1 83. The method of claim 55, further comprising a mutation of a gene,
2 wherein the mutation increases the immune response to autoantigen.

1 84. The method of claim 83, wherein the mutation is the inactivation of the
2 Fc-gamma IIB gene.

1 85. The method of claim 59, further comprising a mutation of a gene,
2 wherein the mutation increases the immune response to autoantigen.

1 86. The method of claim 85, wherein the mutation is the inactivation of the
2 Fc-gamma IIB gene.

1 87. The method of claim 60, further comprising a mutation of a gene,
2 wherein the mutation increases the immune response to autoantigen.

1 88. The method of claim 87, wherein the mutation is the inactivation of the
2 Fc-gamma IIB gene.

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